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Review article

Discovered cancers at postmortem donor examination: A starting point for quality improvement of donor assessment

Ilaria Girolami [a], Desley Neil [b], Dorry Lidor Segev [c], Lucrezia Furian [d], Gianluigi Zaza [e], Ugo Boggi [f], Giovanni Gambaro [e], Tullia De Feo [g], Marilena Casartelli-Liviero [h], Massimo Cardillo [i], Letizia Lombardini [i], Laura Zampicinini [h], Antonietta D'Errico [j], Albino Eccher [k,*]

[a] Division of Pathology, Central Hospital Bolzano, Bolzano, Italy
[b] Department of Cellular Pathology, Queen Elizabeth Hospital Birmingham, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[c] Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[d] Kidney and Pancreas Transplantation Unit, Department of Surgical, Oncological and Gastroenterological Sciences, University and Hospital Trust of Padua, Padua, Italy
[e] Renal Unit, University and Hospital Trust of Verona, Verona, Italy
[f] Division of General and Transplant Surgery, University of Pisa, Pisa, Italy
[g] North Italy Transplant Program, Coordinamento Trapianti, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Cà Granda, Ospedale Maggiore Policlinico, Milan, Italy
[h] Neurosurgery and Intensive Care Unit, Department of Surgical Science, University and Hospital Trust of Verona, Verona, Italy
[i] National Transplant Center, Rome, Italy
[j] Pathology Unit, University of Bologna, IRCCS Policlinico St. Orsola-Malpighi Hospital, Bologna, Italy
[k] Department of Pathology and Diagnostics, University and Hospital Trust of Verona, Verona, Italy

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ABSTRACT

Background: clinical and imaging investigations allow a detailed assessment of an organ donor, but a quota of cancer still elude detection. Complete autopsy of donors is even less frequently performed, due to economic issues and increasing availability of high-quality imaging. The aim of this study is to gather evidence from the literature on donor malignancy discovered at autopsy following organ donation and to discuss the utility and limitations of autopsy practice in the field of transplantation.
Methods: A systematic search according to PRISMA guidelines was carried out in Pubmed and Embase databases until September 2020 to select articles with reporting of cancer discovered in a donor at postmortem examination. Cancer discover in not-transplant setting were excluded. A descriptive synthesis was provided.
Results: Of 7388 articles after duplicates removal, 56 were included. Fifty-one studies reported on complete autopsy, while 5 dealt only with limited autopsy (prostate and central nervous system). The number of autopsies ranged between 1 and 246 with a total of 823 autopsies performed. The most frequent cancer discovered at autopsy was lymphoma ($n = 13$, 15%), followed by renal cell carcinoma (RCC) ($n = 11$, 13%), non-small cell lung cancer (NSCLC) ($n = 10$, 11%), melanoma ($n = 10$, 11%), choriocarcinoma ($n = 6$, 7%) and glioblastoma (GBM) ($n = 6$, 7%).
Conclusions: Lymphoma and melanoma are still difficult-to-detect cancers both during donor investigation and at procurement, whilst prostate cancer and choriocarcinoma are almost always easily detected nowadays thank to blood markers and clinical examination. There have been improvements with time in pre-donation detection procedures which are now working well, particularly when complete imaging investigations are performed, given that detection rate of CT/MRI is high and accurate. Autopsy can play a role to help to establish the correct donor management pathways in case of cancer discover. Furthermore, it helps to better understand which cancers are still eluding detection and consequently to refine guidelines' assessment procedures.

Contents

* Corresponding author at: Department of Pathology and Diagnostics, University and Hospital Trust of Verona, P.le Stefani n. 1, 37126 Verona, Italy.
E-mail address: albino.eccher@aovr.veneto.it (A. Eccher).

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1. Introduction

Transplantation of an organ from a donor carries an unavoidable risk of transmission of malignancy and the risk is increasing with the increasing age of potential donors. Different types of malignant lesions have differing risks of transmission which have led to the development of international guidelines and recommendations to guide the evaluation of a donor with malignancy and to define the risk of transmission for the recipient [1–5]. Donors with a known history of malignancy, either recent or past, trigger increased suspicion and assessment pathways. In addition to donors with a history of malignancy, malignant lesions are discovered during donor' evaluation, both before and during the procurement phase and after transplantation, when an autopsy is performed on the donor. The frequency of performing an autopsy has decreased significantly both in general and for donor assessment [6,7]. The reason for the declining autopsy rate is multifactorial, and varies around the world: the cost of performing an autopsy [7,8]; medical staff failing to think about/discuss an autopsy with family; reluctance of the donor's family; together with the greater availability of imaging techniques, which are now also replacing traditional autopsies [9]. Despite the increasing reliance on radiology/clinical diagnosis, this combined process is imperfect, with the combined diagnosis/cause of death being wrong compare to autopsy findings in 10–27% [7,10–12]. Autopsy confirmed and typed a suspected malignancy in 1.2% [13]. An unsuspected malignancy was found in 8–18% [10,13], worrying in the setting of organ donors, particularly with the increasing age of donors.

The aim of this study is to gather all the published evidence on donor malignancy discovered at autopsy following organ donation and to discuss the utility and limitations of autopsy practice in the field of transplantation. A reassessment of these cases in the current era, taking into account ethical and economic issues, may help to further refine the optimum donor assessment pathways.

2. Materials and methods

We conducted a systematic review according to standard methods and reporting in accordance with the appropriate guidelines, Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [14] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) [15].

2.1. Search strategy and article screening

A systematic search was carried out without any language restrictions in the electronic databases Pubmed and Embase until March 2020 to identify any study documenting the discovery of a malignancy in a donor or in a potential donor. The key terms “autopsy”, “post-mortem”, “donor”, “organ” and “transplantation” were adequately combined in their variations for the two databases. The complete search strategies are found in Supplementary Material - Appendix S1.

Two investigators (IG, SM) independently screened titles and abstracts for eligibility with the aid of Rayyan QCRI reference manager web application [16]. Disagreement was resolved by consultation of the senior researcher (AE). Full-texts assessed for eligibility underwent also reference hand-searching to identify relevant articles potentially missed by the search. Inclusion criteria were the presence of at least one donor or potential donor of organs or tissues where cancer was discovered by means of an autopsy after transplant or after procurement, irrespective of whether organs or tissues were transplanted or of outcome of the recipients. When limited information was present, or it was stated only that cancer was discovered after transplantation, we assumed that it could have been discovered with autopsy of the donor. A limited autopsy of the central nervous system or prostate only were considered separately from reporting of complete whole autopsy cases. When autopsy was performed but excluded a cancer or confirmed a cancer suspected during donor evaluation the paper was excluded.

Full-texts of the articles fulfilling the initial screening criteria were acquired and reviewed for subsequent inclusion, against the eligibility criteria, with the consultation of the third reviewer in case of disagreement.

2.2. Data extraction

Two authors (IG, SM) independently extracted data from the included studies following a standardized extraction form. Data extracted were: type of publication (full paper, abstract or conference communication), author, year and country of study, number of donors, number of donors with cancer, number of cancers discovered at procurement, number of autopsies performed, number of cancers discovered at autopsy, whether donor underwent clinical and/or imaging investigations and which ones, type and site of discovered cancer, which organs or tissues were transplanted, outcome of recipients where present in terms of transmission of malignancy.

2.3. Quality assessment

The quality of studies was assessed independently by two authors and disagreements were resolved by consultation of the third reviewer according to a standardized checklist for quality assessment of case reports and case series [17]. The specific items of the checklist were modified, given that not all the studies were likely to focus primarily on autopsy, but they would likely be case reports of transmission events or retrospective observational studies with descriptive information on a population of donors.

2.4. Data synthesis

A descriptive synthesis of absolute and relative frequencies of discovered cancers was provided with numerical values and percentages. Continuous measures were expressed as median and range, while dichotomous variables were expressed as numerical values and percentages.

3. Results

3.1. Literature search

Of 7388 articles, after duplicates removal, 6863 were excluded after the tile and abstract screening. The remaining 525 were assessed in full-text form and of these 56 were included. The flow of article screening and inclusion is depicted in Fig. 1.

3.2. Quality appraisal

Over 70% of the studies clearly reported the post-mortem identification of malignancy in the donor, the pathological diagnosis and the organs transplanted and their outcome, whilst clear reporting of demographic data of donors occurred in about 60% of studies. On the contrary, only 27% of studies clearly reported whether imaging had been undertaken in the donor and if so, which techniques were performed, whilst this information was completely lacking in more than 60% of the studies. A graphical depiction of the quality appraisal is found in Suppl Fig. S1.

3.3. Characteristics of studies

The included studies comprised 51 full articles, four abstracts and one letter to the editor. The countries represented were European countries in 34 (61%), United States in 18 (32%), Australia in 2 (4%) and Asian countries in 2 (4%). Studies were published in the timespan 1972–2019, with 19 (34%) in the last decade. Half the studies (28, 50%) were case reports of a single donor, 19 (33%) were retrospective studies with larger series of donors ranging from 42 to 14,986 donors, seven studies (13%) were small cases series with less than 20 donors, and in two cases (4%) the exact number of the donors was not provided.

3.4. Frequency of donors, donors with cancer and autopsies

The number of donors ranged between 1 and 14,986 (median 1, mean 871.2 ± 2623.3) with a total of 42,694 donors. The number of donors with cancer ranged between 1 and 377 (median 1, mean 34.8 ± 81.6) with a total of 1704 donors with cancer. In most cases the cancers were known about at time of transplantation, either from the donor history or investigations before the procurement. The number of autopsies ranged between 1 and 246 (median 1, mean 17.9 ± 47.8) with a total of 823 autopsies performed. In 51 studies there was a whole-body

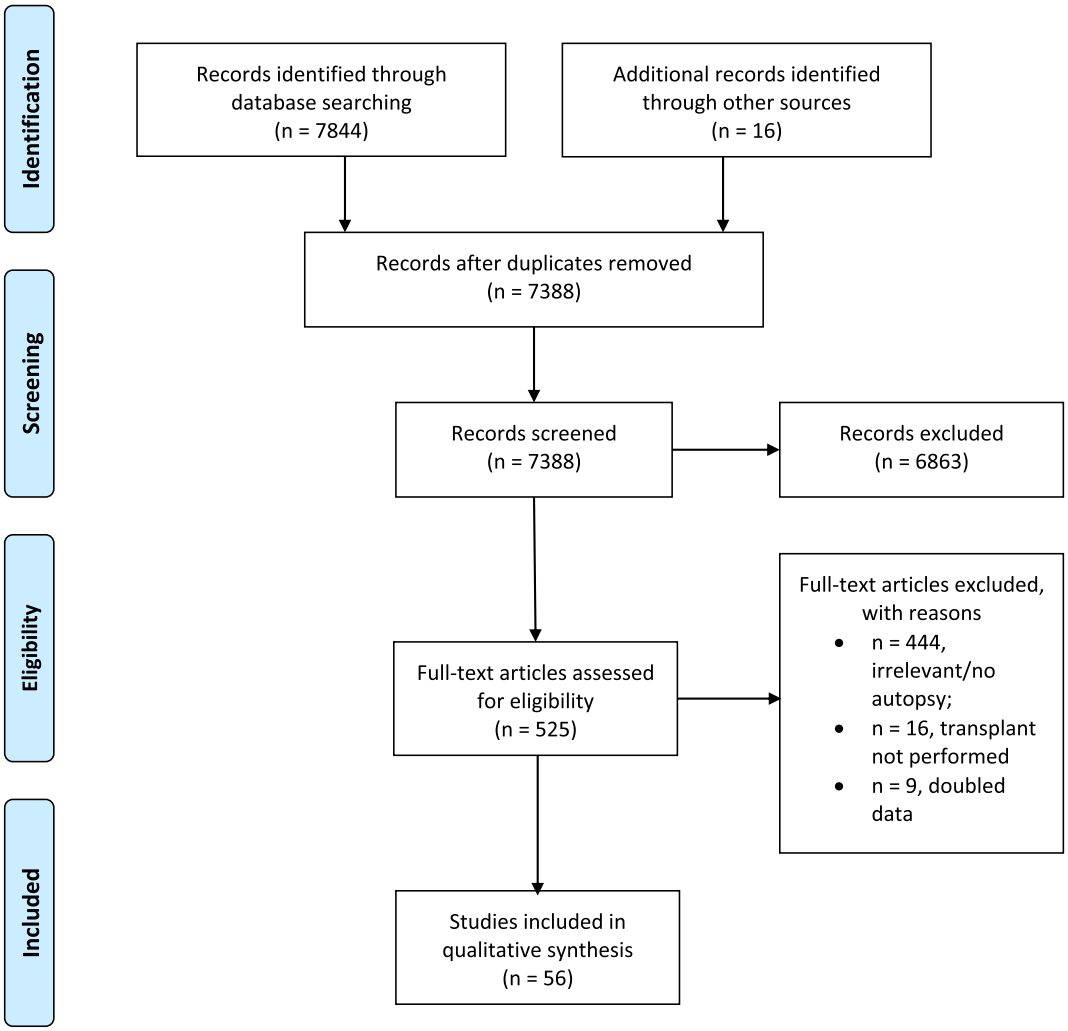

Fig. 1. Search flow of article screening according to PRISMA.

autopsy, in 5 cases there was a limited autopsy, of which in 4 of the prostates and in 1 of the CNS.

3.5. Frequency of cancers discovered at procurement and at whole autopsy

The majority of unsuspected malignancies were identified at procurement with a total of 277, with further 163 identified at autopsy. The number discovered at procurement ranged between 0 and 124 (median 0, mean 6.3 ± 20.1) whilst the number discovered at autopsy ranged between 1 and 29 (median 1, mean 3.2 ± 5.6). Of these performed autopsies an unsuspected malignancy was identified in nearly 20%, however this is likely to be a too high as in some studies the exact number of autopsies is not stated or only the number of autopsies in which a cancer was identified was given. The histological type of tumor was clearly provided in only 91 cases (56%), with no indication as to the type of tumor in some.

The most frequent cancer discovered at autopsy was lymphoma ($n = 13$, 15%), followed by renal cell carcinoma (RCC) ($n = 11$, 13%), non-small cell lung cancer (NSCLC) ($n = 10$, 11%), melanoma ($n = 10$, 11%), choriocarcinoma ($n = 6$, 7%) and glioblastoma (GBM) ($n = 6$, 7%). A complete summary of cancers discovered with whole autopsy with available data is found in Table 1.

3.6. Limited autopsies

There were four studies [18–21] limited to autopsy assessment of the prostate gland with a median number of donors of 148 (range 11–340), a median number of donors with prostate cancer of 12.5 (range 1–41) and a median number of cancers which were specifically discovered at the post-transplant/limited autopsy of 6.5 (range 1–41). In these studies, the prostate was studied after the removal of organs or tissues and there were no transmission events in the recipients. The PSA levels were reported in summary in three studies [18–20], and there was not a statistically significant difference in cancer detection rates between donors with higher or normal PSA levels, and all conclude that PSA alone is not sufficient to guide evaluation of the donor, but clinical exam and possibly prostate organ examination is more useful.

One study [22] focused on the limited autopsy of the CNS where definitive diagnosis was available after organ recovery. Of 8 donors, 7 had a primary CNS tumor of which 5 considered "benign/low risk" by the authors and the transplant went ahead, whilst in the case of the glioblastoma the transplant procedure was canceled.

The studies with limited autopsy are summarized in Table 2.

Table 1
Summary of cancers discovered with whole autopsy.

Cancer type	N	Demographic data	Donor study	Clinico-pathological details	Organs transplanted	Outcome
Lymphoma	13	6 M, 2 F, 5 NA 19–70 years	MRI in 1 case, NA for others	8 NHL NOS, 1 intravascular, 1 CLL, 1 DLBCL, 1 CNS NHL, 1 T lymphoblastic	1 heart, 1 liver, tissue grafts, 15 kidneys, NA for others	Transmission in 10 cases, no transmission in 4 cases, NA for others
Renal cell carcinoma	11	1 M, 10 NA Age NA	NA	11 RCC NOS	4 kidneys, 2 lungs, 1 heart, tissue grafts, NA for others	Transmission in 4 cases, no transmission in 2, NA for others
Non-small cell lung cancer	10	4 M, 2 F, 4 NA 36–75 years	CRX and CT in 2 cases, NA for others	5 adenocarcinoma, 5 NOS	7 kidneys, 1 liver, 1 heart, 1 NA	Transmission in 6 cases, explanted kidneys in 2, NA for others
Melanoma	10	2 M, NA for others Age NA	NA	CNS mtx in 4 cases, spleen mtx in 1 case	7 kidney, 1 liver, 2 heart	Transmission in 6 cases, explant in 1 case, no transmission in 1 case, NA for others
Choriocarcinoma	6	6 F 26–30 years	NA	CNS mtx in 3 cases	4 kidneys, 2 liver, 2 heart, 2 lungs, 1 pancreas	Transmission in all cases
Glioblastoma	6	2 M, 4 NA 46–47 years	CRX and CT in 1 case, NA for others	None of the GBM was known before donation	2 lung, 1 liver, 1 multiorgan, 2 NA	Transmission to the lung recipients
Sarcoma	5	2 M 1F, 2 NA 43–48 years	MRI in 1 case	3 angiosarcoma, 1 fibrosarcoma, 1 sarcoma NOS	2 lung, 2 kidney, 1 cornea, 1 liver, 1 heart	3 explanted, no transmission in 1 case, NA for others
Prostate	5	53–71 years	NA	Mtx in 1 case, size 0.5–1.3 cm in 2 cases	1 heart, 2 liver 2 NA	Transmission in the heart recipient
Breast cancer	3	NA	CRX, US and CT in 2 cases, 1 NA	Size 0.3–0.5 cm in 2 cases, 1 ductal, 1 lobular 1 NA	4 kidneys, 1 liver, 1 NA	NA
Other	22	7 M, 3 F, 12 NA 1–61 years	Total body CT in 1 case, NA for others	3 NET 2 pheocromocytoma 2 plasmacytoma 2 HCC 2 SCC cervix 2 meningioma 1 PTC 1 MTC 1 cholangiocarcinoma 1 myeloma 1 ALL 1 PNET 1 myxoma 1 mesothelioma 1 liver cancer NOS	5 tissue donors, 15 kidneys, 4 heart, 2 liver, NA for others	Transmission in 3 cases (PNET, mesothelioma, high grade meningioma), 3 explants, NA for others

ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CRX, chest radiography; CT, computed tomography; DLBCL, diffuse large B cell lymphoma; F, female; GBM, glioblastoma; HCC, hepatocellular carcinoma; M, male; MRI, magnetic resonance imaging; MTC, medullary thyroid carcinoma; mtx, metastasis; NA, not available; NHL, non-Hodgkin lymphoma; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; PNET, primitive neuroectoderma tumor; PTC, papillary thyroid carcinoma; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; US, ultrasound examination.

Table 2
Summary of studies with limited autopsies.

Author, year (Country)	Total donors	Demographic data of donors	Donor study	N limited autopsies	N cancer discovered at autopsy	Details of cancer	Organs transplanted and outcome
Prostate							
Frutos, 2003 (Spain)	11	Mean age 62.5 years, range 38–73 years	PSA	9	1	Gleason 7, 2.2 cm	1 liver and 2 kidneys; one kidney removed prophylactically
Gonzalez-Segura, 2003 (Spain)	224	Mean age 60.9 years	CRX, US, PSA, DRE	13	6	NS	2 livers and 4 kidneys; no transmission
Skalski, 2018 (Poland)	72	Median age 63 years	PSA, DRE	NS	7	14 Gleason ≤6 5 Gleason >6 9 multifocal	7 livers; no transmission
Yin, 2008 (USA)	340	Range 27–81 years	NS	340	41	Size range 0.2–2.3 cm; 34% multifocal; Gleason range 6–8	No info
CNS							
Meysam/Sadegh-Beige, 2017 (Iran)	8	7 F, 1 M; range 15–52 years	MRI	8	7	1 GBM 1 medulloblastoma 2 astrocytoma 1 meningioma 1 craniopharyngioma 1 neurofibroma	Transplant canceled for the GBM; no data for the other recipients

CNS, central nervous system; CRX, chest radiography; DRE, digital rectal examination; F, female; GBM, glioblastoma; M, male; MRI, magnetic resonance imaging; NS, not specified, PSA, prostate specific antigen, US, ultrasound.

4. Discussion

The most frequent cancers discovered in donors at autopsy are lymphoma, renal cell carcinoma, non-small cell lung cancer and melanoma, followed by choriocarcinoma and glioblastoma. Lymphoma and melanoma are difficult-to-detect cancers as they did not usually present as detectable masses or with clear-cut alterations in routine blood tests. There is no unique strategy to increase the detection rate of these malignancies: for example, a dermatologic examination of the donor can find suspicious skin lesions, while a whole-body CT could highlight enlarged lymph nodes to be searched for during surgical exploration and then sent to the on-call pathologist for frozen section examination, however a frozen section can only diagnose a high grade lymphoma and cannot exclude a low grade lymphoma – this may lead to loss of organs if overzealous use. The relatively higher number of renal cell carcinomas and lung cancer occurred before 2000 when use of CT imaging was not as widespread as at present day. Of note the "recent" missed lung cancers were from abdominal organ only donations where no thoracic exploration was made at procurement [23,24]. This should not be surprising, as abdominal organs are donated more often than thoracic ones. The "recent" missed RCC was from a tissue graft donor, from a large series where no information on donor investigation was provided [25,26]. The near complete absence of undetected choriocarcinoma in the last 25 years highlights the important role of imaging and blood tests [27–29]. The recent case of unsuspected choriocarcinoma occurred when betaHCG testing was not undertaken in a pregnant female who died from a bleed from a presumed vascular malformation [30]. Glioblastoma is another important cause of death, with a significant risk of transmission to recipients that should be suspected in young donors dying of cerebral hemorrhage events [31–35]. Where neuroradiology is not available, then the risks of using a cardiovascular accidents (CVA) donor with no risk factors should be carefully considered, an autopsy limited to the brain could help to determine the presence and the type of tumor and then define the level of risk, however this service may not be widely available. GBM biomarkers are being developed and may be helpful in donor screening in the future [36]. Rather surprisingly there is no documented detection of an unsuspected gastrointestinal malignancy despite its high frequency in the general population. Transmission of GI malignancy does occur but is rare considering the incidence in the general public, but the few that have been picked up following transmission to the transplanted livers have been successfully treated by retransplant [37].

Prostate adenocarcinoma is an incidental finding in autopsies, with the increasing age of the donor pool there is an increasing chance of an incidental prostate carcinoma being present. To try to detect these in male donors a prostatic specific antigen (PSA) and digital rectal examination is performed, with slight protocol differences between countries [4,38,39]. The estimated incidence of prostate cancer identified in donors, either diagnosed at procurement or after transplant, is between 3% and 18.5% [40] and risk of transmission relates to the Gleason grade and staging. We found that in those detected at autopsy following transplantation there was no cancer transmission, the only described transmission was in a cardiac transplant recipient in whom the transplantation procedure was nearly complete when enlarged pelvic lymph nodes were discovered during abdominal organ retrieval, a frozen section showed metastatic adenocarcinoma, subsequent autopsy found advanced high grade and stage carcinoma of the prostate [41].

A major limitation of this study is the inability to be able to determine the incidence of an unsuspected malignancy being identified at autopsy. The relatively high rate of first diagnosis of a donor malignancy during autopsy after organ donation and transplantation (163/823, 19.8%) identified in this review is almost certainly an overestimate because the total number of autopsies is not reported in many papers, just the number of autopsies in which malignancy was identified. Further bias is likely due to reporting positive rather than negative findings. Other issues that interfere with interpretation relate to the lack of complete information and methodology being presented [42]. Other confounding factors include autopsies done as part of research studies and for epidemiological purposes and whether a review of registry data [25,29]. This review highlights that a proportion of cancers still elude the donor investigations being found and defined only at post-mortem. In this relatively small proportion of recipients the discovery of a malignancy at autopsy allows early and individualized management/treatment. It is however not feasible to routinely perform an autopsy on all donors: there would be significant costs in terms of personnel and biological material handling, including the requirement of increased pathologists to be able to undertake this number of postmortems without significant delay to routine diagnostic activity [7,8]. The potential loss of donors related to a

reluctance of the donor's family to have an autopsy performed must also be taken into account. Whilst imaging techniques are not perfect [43], they are increasingly replacing traditional autopsies [9,44]. Imaging techniques are getting more sophisticated [11], and ability to digitally share images for consultation has the potential to maximize the pick-up of unsuspected malignancies prior to transplantation. A recent retrospective radiological series of 1644 donors found that screening of the donor with whole-body CT did miss any lesions detected at the donor retrieval operation, whereas chest x-rays and abdominal ultrasound did. As would be expected not all suspicious lesions detected by CT turned out to be malignant and biopsy was required to assess. The identification of a suspicious lesion ahead of surgery allows advance warning to pathologists to organize their schedules rather than a "come now" phone call. The authors concluded that the increased costs was outweighed by decreasing the duration of the donation procedure and by minimizing the emotional burden for the relatives of the donor by identifying possible contraindications prior to procurement [43]. Further studies comparing imaging and laboratory testing against the findings of an autopsy, the gold standard, would help to answer many questions, but it is recognized that this is unlikely to occur in any systematic manner, not least due to the wishes of the family. Furthermore, considering the poor prognosis of a donor-transmitted cancer [37,45], it would be reasonable to make any effort to prevent this and detect malignancies as more as possible before procurement. Similar considerations are also present in a study included [46], where a structured procedure of donor evaluation which comprised whole-body CT allowed the detection of 32 malignancies out of 400 donors, with only 3 cancers missed and detected at post-mortem examination which were however not mass-forming breast and liver cancer sized less than 9 mm. However, autopsy still retains its value as it can lead to the discovering of an unsuspected cancer, particularly for malignancies difficult to detect with routine available imaging techniques such as lymphoma and melanoma [42,47,48]. Reservation of autopsy procedure to difficult and highly doubtful cases would balance the ethical duty to prevent any harm to the recipient by discovering the cancer in a donor and the need for control the costs and the correct allocation of human and economic resources.

There have been improvements with time in pre-donation detection procedures which are now working well, particularly when complete imaging investigations are performed, because, even with the ongoing incomplete pick up on current advance imaging, the combined clinical, serological, radiological and histopathological pathways detect the vast majority of donors at risk of transmitting a malignancy. In summary, to identify unsuspected donor malignancies with the potential for transmission to the recipient an autopsy would need to be performed in specific donors' setting as is not a feasible option in all organ donors. Autopsy indeed can represent another level of evidence to detect cancer particularly in difficult cases and can help to better understand which cancers are still eluding detection and consequently to refine the detection procedures, e.g. imaging procedures, new diagnostic markers or targeted clinical investigations.

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Declaration of Competing Interest

None.

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